REMARKS/ARGUMENTS

The non-final Office Action of September 20, 2007 has been carefully considered and these amendments and remarks are responsive thereto. New claim 29 has been added to claim a method for relieving discomfort associated with acute, painful musculo-skeletal conditions comprising orally administering a pharmaceutical composition with the same features as pending composition claim 1. No new matter has been added and the Applicants respectfully submit that the claims are in condition for allowance.

Amendment to the Specification

The specification has been amended to describe the subject matter of the New Drug Application No. 13-217, which is a synonym for the product "Skelaxin®." In accordance with the suggestion in the Office Action, the specification has been amended to adequately describe the subject matter set forth in "New Drug Application No. 13-217" in generic terms. Indeed, the amendment to the specification now quotes language from papers of record in the FDA in connection with New Drug Application No. 13-217 (*see* **Annexure 1**). No new matter has been added by this amendment to the specification as shown by the following:

- The only commercially available metaxalone composition at the time the instant application was filed was Skelaxin®, which has NDA No. 13-217, a fact known in the art and available on Orange Book listing.
- Skelaxin® and "commercially available metaxalone composition" have been equated with each other and described throughout the specification.
- The disclosure of Skelaxin® inherently discloses NDA No. 13-217.
- The specification need not provide in 'haec verba' support for the language added to the claim. In order to comply with the written description requirement, the specification "need not describe the claimed subject matter in exactly the same terms as used in the claims; it must simply indicate to persons skilled in the art that as of the date the applicant had invented what is now claimed." *All Dental Prodx LLC v. Advantage Dental Prods., Inc.*, 309 F.3d 774, 779, 64 USPQ2d 1945, 1948 (Fed. Cir. 2002), quoting

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Eiselstein v. Frank, 52 F.3d at 1038, 34 USPQ2d at 1470 (citing *Vas-Cath*, 935 F.2d at 1562, 19 USPQ2d at 1115, and *In re Wertheim*, 541 F.2d 257, 265, 191 USPQ 90, 98 (CCPA 1976)).

- The substitution of NDA No. 13-217 is exactly the type of amendment permitted by M.P.E.P. 2163.07 I., which specifies that "a rewording of a passage where the same meaning remains intact is permissible." *In re Anderson*, 471 F.2d 1237, 176 USPQ 331 (CCPA 1973). *See also Scarring Corp. v. Megan, Inc.*, 222 F.3d 1347, 1352-53, 55 USPQ2d 1650, 1654 (Fed. Cir. 2000) (quoted in the M.P.E.P). In *Scarring*, the original disclosure drawn to recombinant DNA molecules utilized the term "leukocyte interferon." After the filing date, a scientific committee abolished the term in favor of "IFN-(a)," since the latter term more specifically identified a particular polypeptide and since the committee found that leukocytes also produced other types of interferon. The court held that the subsequent amendment to the specification and claims substituting the term "IFN-(a)" for "leukocyte interferon" merely renamed the invention and did not constitute new matter.

The specification has been amended to clarify the term "enhanced bioavailability" in connection with an increase in rate and extent of absorption. There is support to the amendment in the specification. Please see the specification as originally filed at page 6, lines 6-8, and also identified as the last line in paragraph [0021] in the corresponding U.S. Pub. No. 2006/0167069): "Bioavailability referred to herein is rate and extent to which the active ingredient, metaxalone, is absorbed into the systemic circulation from the pharmaceutical composition of the present invention." Support is also found in the specification as originally filed at page 11, lines 1-4, and also identified in paragraph [0039] in the corresponding U.S. Pub. No. 2006/0167069): "As is evident from the table, the metaxalone composition of the present invention gave significantly higher peak plasma concentration, which was achieved more rapidly than with the reference product. The bioavailability, as measured by the area under the plasma concentration – time profile, was significantly higher for the pharmaceutical composition of the present invention as compared to the reference product."

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Rejections under 35 USC 112

In the non-final Office Action mailed September 20, 2007, claims 1, 3-18 and 23 were rejected under 35 § U.S.C. 112, first paragraph, as failing to comply with the written description. Specifically, the rejection contends that the specification does not adequately describe the subject matter set forth in "New Drug Application No. 13-217" in generic terms. As noted above, by this response, the first paragraph of the Detailed Description of the Invention (which is also identified as paragraph [0010] of corresponding U.S. Pub. No. 2006/0167069) has been amended to describe of the New Drug Application No. 13-217 disclosure, and no new matter has been added.

Claim 8 was rejected under 35 § U.S.C. 112, second paragraph, for including the allegedly unclear phrase "has enhanced oral bioavailability," which is already recited in claim 1. Claim 8 has been amended to recite the following: "A pharmaceutical composition as claimed in claim 1, wherein the metaxalone comprises the following particle size distribution characteristics: 99% undersize value between 10 and 40μm in diameter~~, characterised in that the pharmaceutical composition has enhanced oral bioavailability~~."

It is respectfully submitted that the amendments to the specification and claim 8 render the Section 112 rejections moot.

Rejections under 35 USC 103(a)

Claims 1, 3-5, 7-18, 23 and 27 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Liversidge et al. U.S. Patent No. 5,145,684 in view of Scaife et al. U.S. Patent No. 6,407,128. Claims 1, 4-7, 15-18 and 23 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Martin et al. U.S. Patent No. 4,344,934 in view of Scaife et al. U.S. Patent No. 6,407,128. The Applicants respectfully disagree and traverse the rejection.

The Office Action asserts that Liversidge discloses methods for increasing the solubility and bioavailability of hydrophobic drugs by formulating them in nanoparticulate (at least 90 percent particles of 400 nm diameter or less), or a crystalline form with a surface modifier, e.g. a surfactant such as sodium lauryl sulfate. Liversidge broadly states that "[t]he invention can be practiced with a wide variety of drug substances." and that "[t]he drug substance must be poorly soluble and dispersible in at least one liquid medium," (Col. 3, lines 38-39 and 40-42), but does not identify metaxalone or any drug similar to metaxalone in terms of chemical structure.

Similarly, Martin is directed to processes for providing high bioavailability for poorly soluble drugs (*see* Abstract of Martin), by drying a mixture of a drug and a water soluble polymer in a solvent and treating the dried mixture with a wetting agent, to obtain a dry solid for oral administration (*see* Col. 3, line 66 through Col. 4, line 4). Martin does not identify metaxalone or any drug similar to metaxalone in terms of chemical structure. Martin discloses compositions of poorly soluble or water insoluble drugs. The poorly soluble drug is mixed with the water soluble polymer in a solvent. After the drug polymer mixture or solution is formed in a solvent, it is dried by spray drying, flash evaporation or air drying to obtain a powdered drug polymer mixture which is then treated with a wetting agent. The bioavailability studies indicate that relative bioavailability of marketed ultramicrosize griseofulvin and spray dried griseofulvin mixtures with PVP or hydroxyl propyl cellulose both treated with SLS is the same. Martin reviews different methods of enhancing bioavailability like mechanical micronization, particle size and surfactant effects, use of PVP for preparing dispersions of drugs, and preparing ultramicrocrystalline forms of drugs.

The Office Action further asserts that while neither Liversidge nor Martin disclose metaxalone, it would have been obvious to one of ordinary skill in the art to use metaxalone as disclosed in Scaife as a drug substance in Liversidge or Martin, allegedly because metaxalone is a hydrophobic drug that would be expected to benefit from increased solubility and bioavailability. U.S. PTO Memorandum of May 3, 2007, from Margaret A. Focarino, Deputy Commissioner for Patent Operations regarding the Supreme Court decision on *KSR Int'l Co. v. Teleflex, Inc.* stated: "[I]t remains necessary to identify the reason why a person of ordinary skill would have combined the prior art elements **in the manner claimed.**" [Emphasis added] The

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Office Action fails to provide a reason why a person of ordinary skill would have combined the prior art elements **in the manner claimed**, because neither Liversidge nor Martin when combined with Scaife fills the vacuum in the prior art, the vacuum being the missing element of any suggestion, express or implicit, of an increase in both the rate and extent of absorption of metaxalone on an "empty stomach."

The Office Action is in error in omitting to consider the unexpectedness of the results, i.e., the enhancement of bioavailability (enhancement of both the rate and extent of absorption) of a specific drug, namely metaxalone, under the specific condition "that the patient is on an empty stomach." The result is unexpected as discussed in this response and particularly in view of the fact that the only previous solution to the problem was recited in Scaife, which solution produced a contrary result (decreased rate of absorption). This error is the result of considering prior art references selectively rather than the prior art as a whole and an interpretation of the term "enhanced bioavailability," which did not consider it as an increase in both the rate and extent of absorption. The term bioavailability as defined in the specification refers to both the rate and extent of the absorption of drugs. In the art, the term "enhanced bioavailability" has not been used in only one way, but the term has been used to refer to either an increase in only the extent of absorption or to an increase in only the rate of absorption or to an increase in both the rate and the extent of absorption. However, in the present specification the term has been defined explicitly to mean an increase in both the rate and extent of absorption of metaxalone as compared to Skelaxin® tablets (New Drug Application No. 13-217). The Applicants have in their earlier arguments presented that the effect of particle size reduction on the bioavailability (which has been defined as rate and extent of absorption in the present invention) of a drug on an empty stomach is not predictable.

The Office Action apparently concedes that Scaife et al. does not teach any particular values for the size of metaxalone particles in the dosage form nor name any particular solubilizing agent. It cannot be disputed that Scaife does not suggest any other form of metaxalone other than the conventional form described in the New Drug Application No. 13-217. The Office Action also does not dispute that Scaife discloses that providing metaxalone in conventional form with food is a satisfactory solution to Scaife's concerns with bioavailability.

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One of ordinary skill in the art, having the benefit of Scaife's "food" solution, would not have been motivated at the time of the present invention to deviate from Scaife and use it in a method such as Liversidge or Martin with specific objectives of an increase in both rate and extent of absorption of metaxalone on an "empty stomach."

It is to be noted that Table II b Column 5 of Scaife states that the Scaife composition when administered to a patient without food has a faster Tmax (Time to reach the peak plasma level of 3.32 hours) and lower AUC numbers than the same composition when administered to a patient with food (Tmax time is 4.29 hours). Thus, Scaife teaches that while the AUC numbers are greater (i.e., extent of absorption) when the Scaife composition is given to a patient with food than without food, it takes longer to reach peak levels (i.e., rate of absorption) when the Scaife composition is given to a patient with food than without food.

Although Scaife (in column 6, lines 36-37 and lines 45-47) concludes that the composition has a higher rate and extent of absorption, such conclusion is incorrect in view of an increase in Tmax upon administration with food. Tmax is a parameter closely related to the rate of absorption and may be used as a simple measure of rate of absorption. (*See* Remington's Pharmaceutical Sciences", 18th Edition, Mack Publishing Company, Easton, Pennsylvania, 1990, page 1455, submitted in an Information Disclosure Statement filed on October 13, 2006).

Generally, Tmax is related to the rate constant of absorption k_a by the equation:

$$Tmax = \frac{2.303}{k_a - K} \log \frac{k_a}{K}$$

K is the rate constant of elimination of drug from the body, and is unaffected by the presence of food. Therefore, changes in Tmax are related to changes in apparent rate constant of absorption.

On the other hand Cmax is given by the equation:

$$Cmax = \frac{F X_0 e^{-KTmax}}{V}$$

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where F is the extent of absorption, X_0 is the dose, V is the volume of distribution, and Tmax the time to peak plasma concentration. (*See* Milo Gibaldi et al., pg 37-38, Equations 1.106 and 1.110, submitted as Exhibit B of the Response dated July 2, 2007).

Therefore, Cmax is dependent on both extent (F) and rate of absorption, i.e., Tmax. An increase in Cmax without a decrease in Tmax may thus be only due to an increase in the extent of absorption, i.e., F. For further background generally regarding the rate and extent of absorption, see Bioavailability and Bioequivalence: General Concepts and Overview, by Prof Richard Bergstrom et al. of Indiana University, posted on the net at: http://medicine.iupui.edu/clinical/F813_spring2006/Q_ClinicalPKF813Lecture16A07March2006BioavailabilityandBioequivalencerevised.pdf, (submitted as Exhibit C of the Response dated July 2, 2007).

On the other hand, Table 8 of the present application shows both a decrease in Tmax (i.e., rate of absorption) and an increase AUC numbers (i.e., extent of absorption) over the Skelaxin composition (i.e., the Scaife composition) when those compositions are administered to patients without food. This is unexpected in view of the teachings of Scaife that increasing the extent of absorption comes by administering the Scaife composition with food also results in an increase in Tmax, i.e., a decrease in the rate of absorption. The Office Action does not rebut these arguments that the Applicants made previously.

The examiner in the present Office Action does not provide any basis to rebut the applicant's previous arguments that there was no reasonable expectation that both rate and the extent of absorption of metaxalone would be enhanced on an empty stomach by following the teachings laid down in Liversidge. It is reiterated that the obviousness test requires that a person of ordinary skill in the art should have a reasonable expectation of success. The Federal Circuit court in *Pfizer v. Apotex*, 480 F.3d, 1348, 1366, 82 U.S.P.Q.2d 1321, 1334 (Fed. Cir. 2007) noted that reasonable expectation of success is not established where the prior art teaches merely to pursue a general approach that seemed promising in the field of experimentation or gave only general guidance as to particular form of the claimed invention or how to achieve it.

The Office Action's proposed combination of Liversidge in view of Scaife is insufficient to establish the test of reasonable expectation of success that a person of ordinary skill in the art would have **from a consideration of the prior art as a whole**. On the other hand prior art as a whole shows that the results of the general technique are unpredictable when applied to a specific drug. Particularly so the unpredictability rises under the specific condition "on an empty stomach". To substantiate the aforesaid, several documents are enlisted herein below that a person of ordinary skill in the art would have had before him to develop expectations of success, failure or uncertainty:

1) Biopharmaceutics and Drug Disposition (England), (Jan-Mar 1984) Vol. 5, pp. 63-74 (**Annexure 2**).

Pharmacokinetic studies were carried out in dogs and human beings in order to evaluate the effect of different factors affecting the bioavailability of etodolac, Page 64 describes the studies performed in dogs and page 66 describes studies in man. In both the studies 400mg of etodolac was given in micronized as well as regular form. The results of the effect of particle size are described on page 68 and demonstrate that micronized etodolac did not result in a statistically significant change in extent of absorption, but only affected the rate of absorption which is evident from the values of AUC, Cmax and Tmax. (See Table 3 page 69).

Accordingly, the Office Action's arguments that teaching imparted by Liversidge or Martin (i.e., in the absence of any reference to metaxalone) and Scaife (i.e., in the absence of any indication of enhanced rate as well as extent of absorption, and with a contrary result as to the "rate of absorption") somehow can be combined together thus enabling a person of ordinary skill in the art to anticipate "with reasonable expectation of success" the result obtained by the claimed invention (increase in **both** rate and extent of absorption on an **empty stomach**) are belied by real world facts.

2) Kahela, P et.al, Acta Pharm. Fenn., (Apr 1978) Vol. 87, pp. 185-188 (**Annexure 3**).

A ground mixture of spironolactone and microcrystalline cellulose was prepared by grinding them in a vibrational ball mill. Formulation A was prepared by grinding a blend of micronized spironolactone and microcrystalline cellulose whereas formulation B was prepared

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without grinding the micronized spironolactone and microcrystalline cellulose. Figure 1 shows that Cmax values of formulation B were higher with larger AUC values than the milled formulation A. The time to peak concentration is shorter for milled formulation A but the amount absorbed from milled formulation A is lower.

Further, Venning, G. R., G. D. Searle Co., Ltd., High Wycombe, in Absorption Distrib. Drugs, Symp., London (1964), Volume Date 1963, 150-6 (**Annexure 4**), reported that particle size within the tablet did not affect the absorption of spironolactone, and it was concluded that some more complex function of the phys. state within the finished tablets was responsible.

Spironolactone, like metaxalone, has a bioavalability which is affected by food (Clin Pharmacol Ther. 1986 Nov; 40(5): 531-6, Overdiek HW, Merkus FW.) (**Annexure 5**), nevertheless no beneficial results were obtained when spironolactone was milled with microcrystalline cellulose as in Kahela et al. or finer particles were included in tablets as in Venning et al..

The aforesaid results are contrary to the Office Action's arguments that the teaching imparted by Liversidge together with Scaife would have lead a person of ordinary skill in the art to have a "reasonable expectation of success" in obtaining the result achieved by the claimed invention (an increase in **both** rate and extent of absorption on an **empty stomach**).

3) "Remington's Pharmaceutical Sciences", 18th Edition, Mack Publishing Company, Easton, Pennsylvania, 1990, page 1437 (A copy of which was submitted in a Supplemental Information Disclosure Statement on October 13, 2006).

This document discloses that "Particle-size reduction may be deleterious for some drug substances. Increasing surface area by milling or other methods may lead to rapid degradation of a compound. Drug substances also may undergo polymorphic transformation during the milling process." The Office Action does not address the arguments previously made and fails to note that Liversidge et al. mills the drug for a very long period, for example a week. A person of skill in the art cannot be imputed with foresight as to whether metaxalone would remain stable when subjected to an energy intensive process such as milling for such a long period.

Further on the same page Remington teaches that:

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"For chloramphenicol, particle size has virtually no effect on the absorption but it significantly affects the rate of appearance of peak blood levels of the drug. After administration of 50 micron particles as well as 200 micron particles peak levels occurred in 1 hour; with 400 micron particles peak levels occurred in 2 hours; with 800 micron particles peak levels occurred in 3 hours. All 4 preparations had the same physiological availability, which implies that the absorption of chloramphenicol occurs uniformly over a major portion of the intestinal tract."

The aforesaid result thus teaches that particle size reduction does not have any appreciable effect on the increase in extent of absorption for the specific drug chloramphenicol, but increases only the rate of absorption. This is contrary to the Office Action's arguments that the teaching imparted by Liversidge together with Scaife would have led a person of ordinary skill in the art to have a "reasonable expectation of success" in obtaining the result achieved by the claimed invention (increase in **both** rate and extent of absorption on an **empty stomach**).

To the best of Applicants' knowledge the effect of particle size reduction on both the rate and extent of absorption of any specific drug in a particular formulation administered on an empty stomach continues to be unpredictable even today as evidenced by the reference below.

4) Journal of Pharmacy and Pharmacology (England), (2006) Vol. 58, pp. 1319-1326. Wong, SM et al. **(Annexure 6)**

The oral bioavailability of bipyramidal griseofulvin particles with a reduced particle size of 2.18 ± 0.12 μm containing a relatively large proportion (12% w/w) of hydrophilic surfactant were compared with control having a particle size 12.61 ± 1.11 μm. The authors concluded that "the rapid and increased drug dissolution in-vitro was not translated to rapid and enhanced absorption in-vivo, and the oral bioavailability of the model drug was found to be the same from the control and from the bipyramidal particles. The poor in-vivo performance of the bipyramidal particles showed that although the dissolution rate of a class II drug is thought to be a good indicator in-vivo bioavailability, this is not always the case."

Thus even though there was reduction in particle size in conjunction with the use of hydrophilic surfactants there was no increase in bioavailability as compared to the control.

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Further, the art teaches that there are many variables that affect absorption. When a drug is administered by oral route the drug given as a solid undergoes dissolution followed by absorption through biological membranes into the systemic circulation. The main processes affecting the bioavailability of a drug are dissolution, permeability, enzymatic metabolism in the gastrointestinal membrane and first pass metabolism by the liver. Various physiological factors reduce the availability of drugs prior to their entry into the systemic circulation. Poor drug bioavailability can result from low drug solubility, low drug permeability, or both, and any metabolism or degradation of the drug before it reaches the circulation. Whether the drug is absorbed uniformly throughout the gastrointestinal tract or is absorbed only from specific regions referred to as "absorption window" is an important factor that may control the effects of particle size reduction on the rate and extent of absorption. Also, the bioavailability is dependent on many drug related factors.

Due to these variable factors affecting bioavailability of a specific drug it is not possible to predict beforehand that reducing the particle size of the specific drug will necessarily lead to enhancement of both rate and extent of absorption. Thus, it cannot be generalized that a micronized form of a specific drug will be expected or not expected to show increased rate as well as increased extent of absorption. In fact, if both the rate and extent of drug were increased it would indeed be an exciting and an unexpected result.

In the absence of a metaxalone specific prior art that would suggest that an increase in both the rate and extent of absorption of metaxalone on an empty stomach would be reasonably expected and in the presence of earlier failure (Scaife) to increase both the rate and extent of absorption of metaxalone, the findings of the present invention of increases in both the rate and extent of absorption of metaxalone on an empty stomach are indeed surprising and deserving of a patent. Metaxalone was first known through United States Patent No. 3,062,827 issued Nov. 6, 1962 and the product Skelaxin® (New Drug Application No. 13-217) was approved long before 1982 as indicated on the website of the USFDA, and yet persons of skill in the art never reached the results achieved by the present invention.

The Office Action overlooks important factors concerning nonobviousness of the claimed invention. The unexpected result of the present invention is enhanced bioavailability even when

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the composition is administered to a patient on an empty stomach. The prior art cited in the Office Action is general and does not suggest the present invention, which is directed specifically to metaxalone in a pharmaceutically acceptable solubility-improved form, or the unexpected results thereof. Further, the pharmaceutical arts are not predictable, particularly when complex biological systems are involved, and it is settled that it is improper to expect that the general teachings or teachings with reference to particular drug may be applied to another drug. *Accord,* MPEP 2164.03, noting predictable factors, such as mechanical or electrical elements, and **unpredictable** factors, such as most chemical reactions and **physiological activity**.

Thus, there is simply no reasonable expectation of success in achieving increased rate and extent of absorption provided in the teachings of prior arts for a particular form of metaxalone when dosed on an empty stomach over that of the commercially available form Skelaxin®.

It is not possible for one skilled in the art, and without stretching the hindsight theory to impermissible limits, to recognize that the composition of the present invention as claimed by the applicants produces **unexpected advantages** with regard to the rate and extent of absorption and bioavailability characteristics.

When the four factors in *Graham v. John Deere* are correctly applied in this case, it is apparent that the claimed invention is non-obvious over the cited art because neither Liversidge nor Martin when combined with Scaife fills the vacuum in the prior art, the vacuum being the missing element of any suggestion, express or implicit, of an increase in both the rate and extent of absorption of metaxalone on an "empty stomach." Scaife only succeeded in improving the extent of absorption of metaxalone but was unsuccessful in increasing the rate of absorption, as can be seen from the Scaife patent. However, it is clear that there is an error in Scaife in correctly recognizing whether in presence of food the rate of absorption increased or decreased. When recognition of the problem itself is unclear to a person of skill in the art, obviousness cannot be found. Conceptualization of the present invention involves recognizing the problem and formulating objectives of making improvements over prior art to provide the benefits of increased rate and extent of absorption of metaxalone on an empty stomach, *i.e.*, the patient is not inconvenienced with the requirement to take food along with the composition. This

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conceptualization is not the work of an ordinary artisan but the work of an inventor and the Office Action overlooks this factor because the Graham factors are not correctly applied. In making the assessment of differences between the prior art and the **claimed** subject matter, 35 **U.S.C.S. § 103** specifically requires consideration of the **claimed invention as a whole [Emphasis Added].** Inventions typically are new combinations of existing principles or features. The "**as a whole**" assessment of an invention under 35 **U.S.C.S. § 103** requires a showing that an artisan of ordinary skill in the art at the time of invention, confronted by the same problems as the inventor and **with no knowledge of the claimed invention [Emphasis Added],** would have selected the various elements from the prior art and combined them in the **claimed** manner. *Princeton Biochemicals, Inc. v. Beckman Coulter, Inc.*, 411 F.3d 1332 (Fed. Cir. 2005.

Moreover, for long there was an **unmet need** for formulations of metaxalone that would provide increased bioavailability when given to a patient on an empty stomach. This unsolved problem has been successfully resolved by the present invention. Further, Scaife fails to recognize the problem overcome by the present invention. The present case is not unlike a "failure of others" when the problem is recognized but attempts to find a solution fail. Objective evidence, or "secondary considerations," of nonobviousness, such as "commercial success, long felt but unsolved needs, [or] failure of others" should be properly considered in an obviousness analysis. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 86 S. Ct. 684 (1966).

Whereas administration of the Scaife composition with food leads to longer time to attain peak plasma level, the present invention does the opposite – *i.e.*, it takes less time to reach the peak plasma level in the present invention.

It is respectfully submitted that the Office Action does not establish a *prima facie* case of obviousness. At the time of the present invention, there was no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to use metaxalone as disclosed in Scaife and modify it in a manner disclosed in Liversidge or Martin for the objectives of obtaining an increase in both the rate and extent of

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absorption of metaxalone on an "empty stomach." In addition, at the time of the present invention, there was no reasonable expectation of success in modifying Liversidge or Martin, and using metaxalone as disclosed in Scaife.

The Office Action does not respond to the argument that on p. 14 of the December 13, 2006 Response, and repeated in the argument on p. 12 of the July 2, 2007 Response that "whether it is in fact possible to obtain such an enhancement of both rate and extent of absorption of a particular drug cannot be predicted." The Office Action does not respond to the argument that "if for example one micronized drug shows improved bioavailability, it does not naturally extend or be extrapolated to metaxalone." The Office Action does not refute that these arguments are supported by the cited excerpts from "Remington's Pharmaceutical Sciences" at pages 14-15 of the December 13, 2006 Response. The Office Action does not respond to the argument that the cited teachings indicate "that there is no correlation between reduced particle size and bioavailability in the unpredictable pharmaceutical arts" and similar recognition in the U.S. Manual of Patent Examining Procedure (MPEP) 2164.03.

The Office Action does not respond to the foregoing understanding of one of ordinary skill in the art. Instead, the Office Action takes a rigid approach by pointing to a teaching in Liversidge or Martin and contending that it would have been obvious to use Scaife with Liversidge or Martin to obtain a new form of metaxalone and that the new form of metaxalone would have enhanced bioavailability on an empty stomach over that taught in the NDA.

Simply put, at the time of the present invention there was no reasonable expectation that metaxalone in a pharmaceutically acceptable solubility-improved form (e.g., micronized metaxalone) would have enhanced oral bioavailability, i.e., increased both rate as well as extent of absorption, as compared to the pharmaceutical composition of metaxalone corresponding to New Drug Application No. 13-217 when they are administered to a patient on an empty stomach.

The present case is analogous to *United States v. Adams*, 383 U.S. 39, 40 (1966), which was recently recited in *KSR v. Teleflex* – the analogy residing in the unexpected or unpredictable results in the present case and *Adams*. In *KSR*, the Court stated that "normal expected progressive innovation" is not an invention, but the present invention does not give something

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expected because the result as explained above is unpredictable. *KSR* therefore supports the patentability of the present invention particularly by reciting *Adams*.

Double Patenting Rejection

Claims 1, 3-18, 23 and 27 were rejected on the ground of non-statutory obvious-type double patenting as being unpatentable over claims 1-41 of USSN 10/502,896 in view of Liversidge et al. U.S. Patent No. 5,145,684. A double patenting of the obviousness type rejection (non-statutory double patenting) is "analogous to [a failure to meet] the non-obviousness requirement of 35 U.S.C. § 103," except that the patent principally underlying the double patenting rejection is not considered prior art. *In re Braithwaite*, 379 F.2d 594, 600 n.4 (C.C.P.A. 1967). Non-statutory double patenting requires one to consider whether the claims in the two applications are obvious variants of each other and for this purpose the disclosure of the other application cannot be used as prior art. This determination involves two steps (1) construing the claim in the earlier application and the claim in the later application and determining the differences between the claims, and (2) determining whether the difference in the subject matter between the two claims render the claims patentably distinct. *See Eli* Lilly & Co. v. Barr Labs., Inc., 251 F.3d 955, 968 (Fed. Cir. 2001). The later claim is not patentably distinct from the earlier claim if it is anticipated by or obvious in the light of the earlier claim. *Id.* The claims in USSN 10/502,896 (earlier claims) are directed to controlled release compositions with slower absorption than provided by the compositions of the instant claims. For example, independent claim 1 of USSN 10/502,896 recites the following:

> 1. An oral controlled release pharmaceutical composition comprising metaxalone, a pharmaceutically acceptable release rate controlling excipient, and pharmaceutically acceptable excipients, wherein the oral controlled release pharmaceutical composition provides peak plasma levels at a time of about 3 hours or more after oral administration of the composition.

Similarly, the only other independent claim of USSN 10/502,896, claim 17, also requires that the peak plasma levels of metaxalone occur at a time of "about 3 hours or more after oral

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administration." In contrast to the claims of USSN 10/502,896, the instant claim 1 of the present application recites:

(1) A pharmaceutical composition comprising metaxalone in a pharmaceutically acceptable solubility-improved form and at least one pharmaceutically acceptable excipient, characterized in that the pharmaceutical composition has enhanced oral bioavailability as compared to the pharmaceutical composition of metaxalone described in New Drug Application No. 13-217 when they are administered to a patient on an empty stomach.

In this case it is sufficient to consider only one difference between the earlier and later claims. As discussed above, the instant specification defines "enhanced bioavailability" as referring to both increased rate and extent of absorption, thus the object of the instant claims to provide faster and greater metaxalone absorption is different from the claims of USSN 10/502,896, which recite a slower rate of metaxalone absorption (the peak plasma levels of metaxalone occur at a time of "about 3 hours or more after oral administration."). The Office Action is in error in concluding that the claims of USSN 10/502,896 recite metaxalone compositions having increased bioavailability" and that the invention of USSN 10/502,896 is "formulated in rapid release composition". The claims of USSN 10/502,896 only recite "peak plasma levels," which a person of skill in art recognizes simply as the maximum concentration achieved in plasma after dosage (there is an initial increase in plasma levels, a peak plasma level is achieved and then plasma levels fall). The claims of USSN 10/502,896 do not allow rapid attainment of peak levels as they do not achieve peak plasma levels in less than about 3 hours after oral administration. Thus, the claim wordings in USSN 10/502,896 are interpreted to mean slow release or controlled release of metaxalone.

According to U.S. PTO Memorandum of May 3, 2007, from Margaret A. Focarino, Deputy Commissioner for Patent Operations regarding the Supreme Court decision on *KSR Int'l Co. v. Teleflex, Inc.* stated: "[I]t remains necessary to identify the reason why a person of ordinary skill would have combined the prior art elements in the manner claimed." The Office Action fails to provide a reason why a person of ordinary skill would have looked to modifying the invention in claims of USSN 10/502,896, which is a slow release or controlled release

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composition. Further, even if one assumes that a person of skill in the art would use the invention of the claims of USSN 10/502,896 on slow or controlled release as the starting point and seek a very different invention, *i.e.*, the present invention on faster and better absorption, then also there is no further reason as to why claims of USSN 10/502,896 should be combined with Liversidge. Liversidge discloses methods for increasing the solubility and bioavailability of hydrophobic drugs by formulating them in a nanoparticulate or a crystalline form with a surface modifier. Liversidge defines bioavailability as only the **extent** of absorption, stating that bioavailability is "the degree to which a drug becomes available to the target tissue after administration," and noting that the dissolution rate of the drug can affect its bioavailability (*See* Col. 1, lines 13-27 of Liversidge). However, Liversidge is completely silent regarding altering the **rate** of absorption, and therefore there would have been no motivation to combine Liversidge with the claims of USSN 10/502,896, which are concerned with providing a controlled release of metaxalone over time. Moreover, the proposed combination would not result in the instant claims. Claims 1, 3-18, 23 and 27 therefore cannot be considered an obvious variation to claims 1-41 of USSN 10/502,896 in view of Liversidge. Another difference between the instant claims and the claims of USSN 10/502,896 is that the instant claims recite that there is an increased rate and extent of absorption of metaxalone **on an empty stomach**. The Office Action ignores the fact that a person of skill in the art would have had no reasonable expectation of success that a particular composition comprising a specific drug metaxalone would have an increased rate and extent of absorption of metaxalone **on an empty stomach**, which is a surprising finding of the present invention. The reasons as discussed above for the 103 rejections apply with equal force to the non-statutory obviousness type double patenting rejection.

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Conclusion

In view of the foregoing, it is respectfully submitted that the pending claims are in condition for allowance. The Examiner is invited to contact the undersigned should it be deemed helpful to facilitate prosecution of the application.

Respectfully submitted,
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